

Bristol-Myers Squibb Pharmaceutical Research Institute

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20 May 2002

**Dockets Management Branch
Food and Drug Administration, HFA-305
5630 Fishers Lane, Room 1061
Rockville, MD 20852**

**Re: Docket No. 02D-0095; Draft Guidance for Industry on Exposure-response Relationships: Study Design, Data Analysis, and Regulatory Applications
[Federal Register Vol. 67; No. 63: 2 April 2002]**

Dear Sir or Madam:

Bristol-Myers Squibb is a diversified worldwide health and personal care company with principal businesses in pharmaceuticals, consumer medicines, nutritionals and medical devices. We are a leader in the research and development of innovative therapies for cardiovascular, metabolic and infectious diseases, neurological disorders, and oncology. In 2001 alone, Bristol-Myers Squibb dedicated \$2.1 billion for pharmaceutical research and development activities. The company has nearly 6,000 scientists and physicians committed to discover and develop best in class therapeutic and preventive agents that extend and enhance human life. Our current pipeline comprises more than 50 compounds under active development.

For these reasons, we are very interested in and well qualified to comment on this FDA proposal to provide guidance for the pharmaceutical industry on exposure-response relationships.

Summary of BMS Comments on Proposal

We commend the U.S. FDA for assembling this thorough and well written document. However, there are several aspects of the proposed guidance that we at Bristol-Myers Squibb respectfully request be given additional consideration. Issues for general consideration include:

1. Clear, concise and unambiguous definition of what constitutes an exposure-response relationship would be useful. Specifically, when does one know that the exposure-response relationship has been established, and that the response variables are related to both efficacy or safety.
2. FDA should consider instituting a procedure to encourage consistent and balanced interpretation of the guidance and to resolve differences in opinion between the sponsor and an individual reviewer regarding whether a valid exposure-response relationship has been established (e.g., establishment of an exposure-response committee).



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3. A common theme in the document includes incorporating the collection of exposure-response information throughout the drug development process, and to analyze the data in order “to look for interesting relationships”. Can guidance be given to the use of meta-analysis techniques in the analyses of these data (e.g., when exposure data are not available in all subjects)?
4. The use of concentration-controlled trials to define the exposure-response relationship is emphasized in this document, despite the inherent difficulties and relative lack of use in drug development. The rationale for this design versus the dose-controlled trial appears biased, and there is literature to substantiate the value of alternate study designs as described in the references below:
 - Levy G, Ebling WF, Forrest A. Concentration- or Effect-controlled Clinical Trials with Sparse Data. *Clin Pharmacol Therap* 1994; 56(1): 1-8.
 - Ebling WF, Levy G. Population Pharmacodynamics: Strategies for Concentration- and Effect-Controlled Clinical Trials. *Ann Pharmacother* 1996; 30(1): 12-19.
 - Ebling WF, Matsumoto, Levy G. Feasibility of effect-controlled clinical trials of drugs with pharmacodynamic hysteresis using sparse data. *Pharm Res* 1996; 13: 1804-1810.
5. Comment is needed regarding instances in which it may be unethical to give low doses to establish the lower portion of the exposure-response relationship for efficacy (eg, in infectious diseases where pharmacodynamically-linked parameters are known and dose can be selected based on pharmacokinetics in healthy volunteers) or to give high doses to establish the upper portion of the exposure-response relationship for safety reasons.
6. Comment on PK/PD modeling with the effect-compartment model, indirect response model and irreversible response model should be included.

Specific Comments (Items that Need Clarification & Recommended Actions)

Line 45-46: “That is, a drug can be determined to be safe and effective only when the relationship of beneficial and adverse effects to a defined exposure is known.” This statement oversimplifies understanding of the exposure-response relationship, particularly when a direct relationship is not evident.

Recommendation: *FDA should consider rewording this sentence to include comments about how useful understanding the exposure-response relationship can be in the assessment of the benefit-risk ratio for changes in exposure.*

Line 80-81: “This section describes uses of exposure-response relationships in drug development and regulatory decision making”. The uses of the exposure-response relationship in drug development are well highlighted in this document, eg, the use of this knowledge in defining the implications of intrinsic and extrinsic factors on exposure and defining the exposure-response implications. However, the use of exposure-response relationships regulatory decision making, specifically in obtaining regulatory approval for a NCE is less well defined.

Recommendation: *FDA should consider providing clear examples of when knowledge of the exposure-response relationship facilitate the approval process, and/or obviate the need for two well-controlled clinical trials.*

Line 139-147: In this paragraph, captopril was cited of an example where understanding the exposure-response relationship could have avoided toxicity.

Recommendation: *FDA should consider using additional examples throughout the document to convey relevant points and increasing the number of literature references in support of selected proposals.*

Line 199-202: “Exposure-response information for a well-understood short-term clinical or pharmacodynamic endpoint.” Clarification on the definition of a “well-understood endpoint” would be useful.

Recommendation: *FDA should consider providing clear definition of the minimum requirements for accepting that a relationship between concentration and biomarker/surrogate/ clinical endpoints has been established.*

Line 347: Recommendation: *The phrase “individual PK variability” should be changed to “inter-individual PK variability”*

Line 351-376: The use of concentration-controlled trials to define the exposure-response relationship is emphasized in this paragraph, despite the inherent difficulties and relative lack of use in drug development. The rationale for this design versus the dose-controlled trial appears biased, and there is literature to substantiate the value of alternate study designs as described in the following reference:

- Levy G, Ebling WF, Forrest A. Concentration- or Effect-controlled Clinical Trials with Sparse Data. *Clin Pharmacol Therap* 1994; 56(1): 1-8.
- Ebling WF, Levy G. Population Pharmacodynamics: Strategies for Concentration- and Effect-Controlled Clinical Trials. *Ann Pharmacother* 1996; 30(1): 12-19.
- Ebling WF, Matsumoto, Levy G. Feasibility of effect-controlled clinical trials of drugs with pharmacodynamic hysteresis using sparse data. *Pharm Res* 1996; 13(12): 1804-1810.

Recommendation: *FDA should consider including a description of and balanced assessment of all relevant study designs, or clearly define that these are examples.*

Line 447-451: “To the extent possible, exposure-response studies should include measurements of the parent drug and its metabolites. Measurement of all active moieties is especially important when....”

Recommendation: *FDA should consider revising the above sentences as follows: ““To the extent possible, exposure response studies should include measurement of the parent drug and major active (or toxic) metabolites that are deemed by the sponsor to be important. This can be especially important when the route.....”*

Line 580: “In many cases, multiple response endpoints are more informative than single endpoints for establishing exposure-response relationships.” Construction of a weighted or combined response that weighs each endpoint relative to biomarker, surrogate and/or clinical benefit may be helpful when interpreting such data.

Recommendation: *FDA should consider including a statement on how to weight the relative importance of multiple (possibly conflicting) endpoints.*

Line 635-638: “However, in general trials examining surrogate endpoints, even when the endpoint is well correlated with a clinical outcome, surrogates will be unable to evaluate clinically relevant effects of the drug not related to the surrogate, whether these are beneficial or adverse (Temple 1999). This sentence is long and unless read closely could be misinterpreted.

Recommendation: *FDA should consider either simplifying the sentence or rewording the comment into two sentences.*

Line 709: “The model selected should be based on the assumption made and the intended use of the model in decision making”. Although one could agree with statement, model selection should be governed by the mechanism of action of the drug, which will lead to the use of, e.g., direct, indirect or irreversible response models.

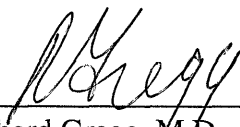
Recommendation: *FDA should consider including a statement that “model selection should be governed by the mechanism of action of the drug, which will lead to the use of, e.g., direct, indirect or irreversible response models.”*

Line 735-738: “The common method for estimating [model] predictability is to split the data set into two parts, build the model based on one set of data, and test the predictability of the resulting model on the second set of data.” This approach to model validation only strictly applies to large data-sets such as obtained in Population PK/PD studies.

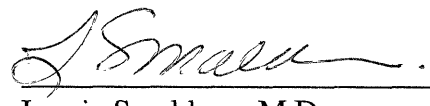
Recommendation: *FDA should provide guidance regarding model validation based on smaller populations of subjects which have undergone intense PK/PD sampling. For example, relationship to mechanism of action and measures of goodness of fit.*

BMS appreciates the opportunity to provide comment and respectfully requests that FDA give consideration to our recommendations. We would be pleased to provide additional pertinent information as may be requested.

Sincerely,



Richard Gregg, M.D.
V.P., Clinical Discovery



Laurie Smaldone, M.D.
Sr. V.P., Global Regulatory Sciences

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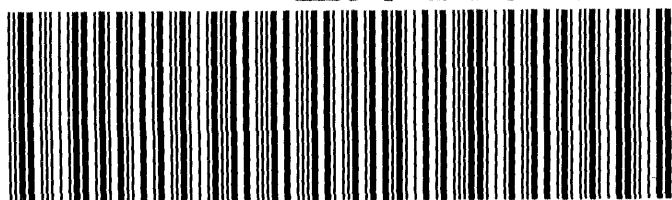
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